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TITLE: Xenon as a Neuroprotectant in Traumatic Brain Injury

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14. ABSTRACT

The purpose of this novel study is to determine if xenon has a neuroprotectant effect in an vivo animal models of TBI. The project scope is an early proof of concept in rat models of xenon neuroprotection. The Specific Aims are to determine the effect of inhaled xenon on brain histopathology, behavior, in short- and long-term fluid percussion (FP) and controlled cortical impact (CCI) rat models of TBI compared to controls. The scope of this project is proof of concept in a rat model. Major findings and progress: We developed a recirculation xenon device for this project. Xenon and devices for behavioral studies acquired. IACUC and VA Research Approvals had been obtained. We believed ACURO approval was in place, but discovered late that it was not. We halted animal work immediately, and re-designed and submitted the appended Statement of Work, which was approved. Animal work generated without ACURO approval cannot be used. ACURO approval will be needed prior to starting this work.

15. SUBJECT TERMS
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INTRODUCTION: Xenon has neuroprotective effects, through blocking multiple neuronal receptors (NMDA, AMPA, kainite and others) to block excitotoxicity, but is also anti-apoptogenic, may regulate cerebral blood flow, blocks excitotoxic dopamine release, and has anti-inflammatory effects, as well as other mechanisms. The progressive secondary neuronal damage from TBI is dependent upon these mechanisms antagonized by xenon. The purpose of this novel study is to determine, at the level of proof of principle, if xenon has a neuroprotectant effect in *in vivo* animal models of TBI.

BODY:

OBJECTIVES/SPECIFIC AIMS. We will test the hypothesis that inhaled xenon administered after TBI reduces neurologic and behavioral deficits in two *in vivo* rat models.

Task 1. Determine the effect of inhaled xenon on brain histopathology in short-term fluid percussion (FP) and controlled cortical impact (CCI) rat models of TBI compared to controls.

1a. Approvals will be obtained from IACUC (BWH) and Research and Development Committee (VAMC) and ACURO.

We have obtained the first two approvals. IACUC and VA Research Approvals had been obtained. We believed ACURO approval was in place, but discovered late that it was not. We halted animal work immediately, and re-designed and submitted the appended Statement of Work (SOW), which was approved. This SOW may require further revision based on the remaining time available in the No Cost Extension that was granted. This would be subject to approval. Animal work generated without ACURO approval cannot be used. ACURO approval will be needed prior to starting this work.

1b. Equipment and xenon procurement. Devices and xenon are in place in Dr. Kristal's laboratory, as described in last year's report.

1c. Methods development. The method of xenon administration has been established in Dr. Kristal's laboratory, and is described in last year's report. Room air has been used instead of oxygen. The milieu within the xenon recirculation chamber is designed to be either 50% xenon/50% room air or room air. *Please see the appended revised Statement of Work regarding Methods.*

1d. Conduct of CCI trials. The method for CCI trials is described in detail in last year's report. *Please see the appended revised Statement of Work regarding Methods.*

Task 2. Determine the effect of inhaled xenon on behavior in short-term fluid percussion (FP) and controlled cortical impact (CCI) rat models of TBI compared to controls. The methodology is described in last year's report. *Please also see the appended revised Statement of Work regarding Methods.*

KEY RESEARCH ACCOMPLISHMENTS:

- Designed and manufactured a unique xenon-recirculation box in which the concentration of xenon and oxygen are reproducibly and accurately controlled and conserved .

REPORTABLE OUTCOMES:

- Designed (primarily by colleague Dr. Jose Venegas) and manufactured a unique xenon-recirculation box in which the concentration of xenon and oxygen are reproducibly and accurately controlled. This can be used for a variety of xenon-related experiments.

CONCLUSION: We have successfully established a reliable and reproducible system for xenon recirculation. Animal work, as described in the revised Statement of Work, is planned to progress once ACURO approval has been obtained.